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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SALIMI, ALI REZA	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 04/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/042,526	GISSMAN ET AL.	
	Examiner	Art Unit	
	A R. Salimi	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/29/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-16 are pending.
Raw Sequence Listing have been entered.
Submitted Information Disclosure Statement (I.D.S) is noted.

Priority

This application filed under former 37 CFR 1.62 lacks the necessary reference to the prior application. A statement reading "This is a continuation of Application No. 09/632,286, filed 8/3/2000, now abandoned, which is a continuation of Application No. 08/944,368 filed 10/6/1997, Patent No. 6, 228,368." should be entered following the title of the invention or as the first sentence of the specification. Also, the current status of the parent nonprovisional application(s), if any, should be included.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,228,368 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. The composition claimed in the ,368 patent encompasses the now claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-16 are rejected under 35 U.S.C. 102(a) as being anticipated by Muller et al (Virology, 1997, Vol. 234, pp. 93-111).

The teaching of Muller et al clearly meets the limitations of claimed invention. They described the formation of Chimeric papilloma virus particles by replacing the 34-carboxy-terminal amino acids of the HPVs (see abstract). In addition they disclosed the fusion proteins similar to the applicants' (see Table 1, page 99).

Claims 1, 15, and 16 are rejected under 35 U.S.C. 102(a) as being anticipated by Lowy et al (US Patent No.5,618,536).

The claims of the ,536 patent meet the limitations of the applicant's claims. Lowy et al taught the fusion of L1 and L2 protein of human papillomavirus and a second protein such as BPV L2. They further disclosed the formation of virus like particles used in an immunogenic composition that can be used for reduction or prevention of papillomavirus. The Patent Office does not have facilities to perform physical comparisons between the claimed product and similar prior art products.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over LI et al (J. Of Virology, Apr. 1997), and Lowy et al (WO 94/05792A) in view of Zhou et al (Virology, 1991, Vol. 185, pp. 625-632).

The claims are directed to antigenic formulations of human papillomavirus (HPV) capsomere L1 protein fused to early HPVs or other proteins wherein the composition would not

form virus like particles (VLP). The claims are also directed to deletion of various parts of carboxyl, amino terminus, or internal residues of all types of L1 genes of variety of HPVs fused to all types of early HPV genes. Also claims are directed to deletion of nuclear localization signal and subsequent formulation utilization as an antigenic formulation. In addition the claims are directed to method of utilizing an antigenic formulation for reducing the level of infection of HPV. In addition, the claims are directed to method of preventing papillomavirus by treating an individual susceptible for infection of HPV.

LI et al disclosed that the trypsin digestion and deletion of carboxy-terminal domain of full length L1 protein yielded pentameric capsomere which self assembled into capsid like particles and not VLPs (see abstract). They further taught that site directed mutagenesis reveled three functional domains of the L1 proteins, specifically the region that affects the formation of capsomere (Page 2992, right column, first full paragraph). They further disclosed the fusion proteins and state of the art with regard to nuclear localization signal sequence (NLS) (page 2994, left column). LI et al taught that L1 purified in the manner disclosed showed similar results to VLPs (pages 2994, right column, last paragraph, and page 2995, left column). This differ since they did not teach fusion of L1 to other proteins.

Lowy et al disclosed recombinant papillomavirus capsid proteins that self assemble to form capsomere structure comprising L1 and /or L1 and L2 (see page 4, lines 12-23, and page 5, lines 20-24). In addition, they disclosed a method of preventing and treating papillomavirus infection (see page 6, lines 20-24). Moreover, they disclosed the fusion of L1 and other proteins such as L2 would induce high titer of neutralizing antibodies and may be useful for treatment of papillomavirus (see page 10, lines 19-24). They disclosed method of producing fusion of L1 and

L2 wherein the protein would yield capsomere or portions thereof would render capsomere (see claims 1-46).

Zhou et al identified the nuclear localization signal (NLS) of human papillomavirus type 16 (HPV-16) L1 protein, and further added that the database search indicated existence of homology among the L1 papillomavirus types with the NLS of HPV-16 L1 (see abstract). They taught that deletion of the NLS would allow the diffusion of enough protein into the cytoplasm and not into the nucleus, with specific reference to the particular amino acids (see page 629, left column 2nd paragraph). This differs from the claims since they did not use their constructs to be used as a vaccine.

Therefore, one of ordinary skilled in the art would have been motivated buy the teaching of prior art to take the L1 protein of papillomavirus and delete the C-terminus and form capsomere as taught by both LI and Lowy et al to induce immune response in a host to reduce infection caused by papilloma virus. In addition, one of ordinary skilled in the art would have been motivated to delete the NLS as taught by Zhou et al for the protein to remain in the cytoplasm. In addition, the disclosure of LI et al also taught the deletion of NLS, since the region is located at the carboy terminus of L1 protein and by deletion of C-terminus, the nuclear localization signal is ineffective . Thus, all of the elements of the claimed invention are taught by the above cited art. Thus, the invention as a whole is considered to be ***prima facie*** obvious absent any unexpected results.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al (US Patent No.5,618,536), and Paintsil et al (Virology, 1996, Vol. 223, pp. 238-244) in view of Zhou et al (Virology, 1991, Vol. 185, pp. 625-632).

The claims are broadly directed to chimeric vaccine formulations of human papillomavirus (HPV) capsomere L1 protein fused to early HPVs or other proteins. The claims are also directed to deletion of various parts of carboxyl, amino terminus, or internal residues of all types of L1 genes of variety of HPVs fused to all types of early HPV genes forming a virus-like particles. The vaccine formulation is further directed to HPV types 6, 11, 16, 18, 33, 35, and 45. Also claims are directed to deletion of nuclear localization signal and subsequent formulation utilization as a vaccine. In addition the claims are directed to method of utilizing a vaccine for treating an individual infected with HPV or reducing the infection of the individual infected with HPV. Plus the claims are directed to method of preventing papillomavirus by treating an individual susceptible for infection with HPV. Lowy et al disclosed the formation of chimeric fusion protein of L1 and L2 and/or HPV16L1 and HPVL2-HPVE7 or BVP L1 and BPV L2-HPV16E7 (see claims 1-24) wherein the chimeric fusion protein were capable of forming virus like particles (VLPs). They described that the VLPs characterized as having conformational epitopes (see column 4 lines 66-67, and column 5 lines 1-2) which would strongly suggests the composition would be able to induce strong antibody response and can be used for preventive method to be administered to "susceptible" individuals. They further disclosed the induction of immune response utilizing the chimeric composition (see claims 14, 15). This differs from the claims since they did not teach the deletion of L1 at various residues

to be able to produce VLPs and utilized in a vaccine. On the other hand, Paintsil et al disclosed and identified areas within the bovine papillomavirus type -1 L1 protein wherein various mutations and deletions were implemented and the constructs were expressed by baculovirus expression systems. Further comparison were made between the virus like particles of wild type BPV L1 expressed in recombinant baculovirus and the mutant constructs. They disclosed that most of the mutants screened showed aggregate formation, but the C-terminal truncation mutant lacking the last 24 amino acids were seen to form VLPs (see abstract). They further disclosed that most capsid or aggregates derived from deletion mutants were unable to show any hemagglutine activity which is indicative of loss of conformational epitopes. Figure 1 (see page 239) disclosed the sequential deletions of the L1 gene and specifies the deleted regions and whether or not they formed any capsomeres or showed any hemagglutination activity (see page 242, left column first paragraph). The further described that the carboxyl-terminus truncation mutant ΔC2 lacking amino acids 471-495 formed into VLPs, indicating that this area is not critical for assembly. They also disclosed, upon further deletion the VLPs did not form indicating that the deletion of more conserved region above amino acid 471 perturbs the folding of the L1 protein (see page 243, right column, 2nd paragraph). Moreover, they compared 12 different L1 papillomavirus C-terminal sequences, many are the same as applicant's, and concluded that truncation of ΔC2 formed capsids while the ΔC1 mutant missing this regions failed to form capsids (see Figure 4). They also disclosed that ΔC2 can tolerate insertions of up to 50 amino acids of HPV-16 E7 protein and still form VLPs. They further added that HPV-16 L1 with a similar C-terminal deletions has also been used for the insertion of HPV-16 E7 sequences and still formed VLPs (see page 243, right column last paragraph). This differs from

the claims since they did not use their formulation to induce protective or preventive response. Zhou et al identified the nuclear localization signal (NLS) of human papillomavirus type 16 (HPV-16) L1 protein, and further added that the database search indicated existence of homology among the L1 papillomavirus types with the NLS of HPV-16 L1 (see abstract). They taught that deletion of the NLS would allow the diffusion of enough protein into the cytoplasm and not into the nucleus, with specific reference to the particular amino acids (see page 629, left column 2nd paragraph). This differs from the claims since they did not use their constructs to be used as a vaccine. However, one ordinary skilled in the art at the time the invention was filed would have been motivated to form chimeric constructs comprising L1 gene of HPVs and early protein or other proteins to be used in a vaccine formulation. The references collectively would have taught the one ordinary skilled in the art where to look for particular deletions of the L1 gene and which parts to avoid for successful formation of VLPs or CVLPs as taught by both Zhou et al and Paintsil et al. The references direct the skilled artisan the areas of importance for the deletions and the homology that exist among the various papillomavirus types of the important regions. The skilled artisan would have been further motivated by teachings of Lowy et al to use the deleted chimeric constructs that form CVLPs and maintained their conformational epitopes to be used as vaccines or immunogenic compositions. Since Lowy et al taught that full length L1 fused to other early genes would be useful in inducing immune response. In addition Paintsil et al had specifically observed and reported that the HPV-16 L1 with deletion in C-terminal fused to E7 protein still formed VLPs. Thus one ordinary skilled in the art would have been motivated to use the teaching of Zhou et al and Paintsil et al, deleted the important regions, and fused the various genes of HPVs as taught by Lowy et al to form chimeric vaccines. One ordinary skilled

in the art being familiar with the cited articles would not have anticipated any unexpected results, since known methods and products render expected results. Therefore, the invention as a whole is considered to be ***prima facie*** obvious absent unexpected results.

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to A. R. Salimi whose telephone number is (571) 272-0909. The examiner can normally be reached on Monday-Friday from 9:00 Am to 6:00 Pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (571) 272-0902. The Official fax number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A. R. Salimi

4/25/2005